

OPEN

# Real-World Observational Review of Andexanet Alfa Prescribing and Utilization Outcomes at a Community Teaching Hospital

**OBJECTIVES:** Andexanet alfa is the first approved antidote in the management of life-threatening bleeds in patients treated with Xa inhibitors. The ANNEXA-4 study was successful in reducing factor Xa levels during time of administration but lacked correlation to improved patient outcomes. Given its novel mechanism of action, U.S. boxed warning, cost of up to \$58,000 per dose, and limited efficacy data compared with standard of care, hospitals are faced with a dilemma with its addition to formulary and process for ensuring optimized use. The objective of this study was to evaluate adherence to institution restriction criteria and the clinical outcomes of treatment for patients for whom andexanet alfa is requested.

**DESIGN:** Retrospective cohort study of andexanet alfa requests within a 12-month time period.

**SETTING:** A 600-bed community teaching hospital.

**PATIENTS:** Patients whom pharmacists received request for dispensing andexanet alfa.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Quality outcomes reviewed compliance to restriction criteria. Clinical outcomes evaluated use of adjunctive blood products, ICU length of stay, hospital length of stay, and hospital mortality. Safety outcomes evaluated incidence of thrombotic events. Andexanet alfa was requested for 16 patients from November 2018 to November 2019. It was administered in nine patients, with compliance to restriction criteria of 66.6%, average ICU length of stay 5.6 days, hospital length of stay 8.6 days, hospital mortality in 44.4%, and thrombotic events in 33.3%. Orders were rejected in seven patients with compliance to restriction criteria of 100%, ICU length of stay 3.2 days, hospital length of stay 5.5 days, hospital mortality in 14%, and thrombotic events in 14%.

**CONCLUSIONS:** A greater rate of adverse effects and mortality was identified with the use of andexanet alfa compared with clinical trials. This is potentially due to its use in a more severely ill patient population and lack of adherence to restriction criteria.

**KEY WORDS:** apixaban; andexanet alfa; formulary; reversal; rivaroxaban; Xa inhibitors

For nearly a decade, factor Xa (FXa) inhibitors have been widely used as oral anticoagulants for various indications (1–3). Despite ease of administration and omission of frequent monitoring, acute life-threatening bleeding remains as a major adverse effect of these agents (3). Until recently,

Kristine A. Sobolewski, PharmD,  
BCPS<sup>1</sup>

Alison Brophy, PharmD, BCPS,  
BCCCP<sup>1</sup>

Seohyun (Claudia) Choi, PharmD,  
BCCCP<sup>2</sup>

Yekaterina Opsha, PharmD,  
BCPS-AQ Cardiology, AACC,  
FHSA<sup>2</sup>

Copyright © 2021 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000000356

**TABLE 1.**  
**Patient Characteristics**

Patient No.	Age	Sex	Estimated Glomerular Filtration Rate	Bleed Presentation Request	Xa Inhibitor	Andexanet Reversal Received	Dose <sup>a</sup> Received	Blood Products Within 24 hr of Reversal	Hospital Mortality	Inpatient Thrombotic Event
1	74	Female	51.37	Reversal for placement of central line	Apixaban	No	NA	None	No	No
2	76	Female	28.17	Presurgical reversal	Apixaban	No	NA	3 U PRBC, 2 units FFP, 1 U platelets	Yes	No
3	48	Female	> 60	Abdominal wall hematoma/left lower quadrant subcutaneous hematoma	Fondaparinux	No	NA	4 U PRBC, 2 units FFP, 1 U platelets, 4F-PCC	No	No
4	72	Male	50	Subdural hematoma	Apixaban	Yes	High dose	4F-PCC (outside facility)	Yes	No
5	88	Female	49.98	Gastrointestinal bleed	Apixaban	No	NA	3 U PRBC	No	No
6	76	Male	> 60	Gastrointestinal bleed	Apixaban	No	NA	2 U PRBC	No	Yes—right lower leg deep vein thrombosis
7	82	Male	> 60	Intraventricular hemorrhage	Apixaban	Yes	Low dose	None	No	No
8	90	Female	18.3	Presurgical reversal	Rivaroxaban	No	NA	4F-PCC	No	No
9	80	Male	60	ICH	Apixaban	Yes	Low dose	None	Yes	No
10	61	Female	28	Subarachnoid hemorrhage	Rivaroxaban	Yes	Low dose	None	No	Yes—MCA infarct day 9
11	88	Female	> 60	Gastrointestinal	Apixaban	Yes	Low dose	3 U PRBC	Yes	Yes—death from MCA infarct < 24 hr after drug
12	86	Male	> 60	ICH	Rivaroxaban	Yes	High dose	None	No	No
13	82	Male	> 60	ICH	Rivaroxaban	No	NA	2 U platelets, 4F-PCC desmopressin	No	No
14	47	Male	> 60	Presurgical reversal	Apixaban	Yes	400 mg bolus only	None	No	No
15	60	Male	> 60	ICH	Rivaroxaban	Yes	Low dose	4F-PCC after andexanet	Yes	Yes—transesophageal echocardiogram left atrial appendage thrombus day 3
16	77	Male	5.27	Gastrointestinal	Apixaban	Yes	Low dose	None—Jehovah's witness	No	No

FFP = fresh frozen plasma, ICH = intracerebral hemorrhage, MCA = middle cerebral artery, NA = not applicable, PRBC = packed red blood cells, 4F-PCC = 4-factor prothrombin complex concentrate.<sup>a</sup>High dose: 800 mg bolus, 960 mg infusion; low dose: 400 mg bolus, 480 mg infusion.

**TABLE 2.**  
**Intracranial Hemorrhage Patient Characteristics**

Patient No.	Age/ Sex	Type of ICH	ICH or SAH Score	Location	Glasgow Coma Scale Score	Intraventricular Blood	Time Between Imaging	Hematoma Expansion	Hospital Mortality	LOS ICU (d)	LOS Hospital (d)
4	72/male	Subdural hematoma	NA	Right hemispheric	3	No	NA	NA	Yes	1	1
7	82/male	ICH	3	Cerebellum	15	Yes	22:40	No	No	11	17.6
9	80/male	IPH, SAH	6	Cerebellum with extensive intraventricular extension	3	Yes	NA	NA	Yes	1	1
10	61/female	SAH	H&H grade 1 Fisher's 1	Perimesence- phalic	14	No	19:00	No	No	13	19
12	86/male	IPH	1	Right thalamic	15	No	5:15	No	No	2	6
13	82/male	IPH	1	Right frontal lobe	14	No	8:10	No	No	4	4
15	60/male	IPH	1	Right parieto- occipital lobe	14	Yes	6:32	No	Yes	14.5	14.5

ICH = intracerebral hemorrhage, LOS = length of stay, NA = not applicable, SAH = subarachnoid hemorrhage.

prothrombin complex concentrates (PCCs) were used off-label for the acute life-threatening bleeding secondary to FXa inhibitors (4, 5). In May 2018, the Food and Drug Administration (FDA)-approved andexanet alfa (Andexxa) as a recombinant modified human decoy FXa protein molecule. It is the first and only available antidote approved by the FDA to manage life-threatening or uncontrolled bleeding specifically associated with the acute use of rivaroxaban or apixaban therapy (6). Despite its novel mechanism of action, this medication carries a U.S. boxed warning for risk of arterial and venous thromboembolic events, ischemic risks, cardiac arrest, and sudden death with drug cost of up to \$58,000 per dose (6, 7). Currently, there are limited data on the evaluation of safety and efficacy of andexanet alfa in comparison with the standard of care, aside from retrospective comparative data. It is also important to note that the ANNEXA-4 study lacked correlation to improved patient outcomes (7, 8). The study noted that no significant relationship existed between hemostatic efficacy and reduction in anti-FXa activity during treatment. The medication was successful in reducing FXa levels during the time of administration (8).

In November 2018, this community teaching hospital added andexanet alfa to the formulary with the following restrictions: life-threatening hemorrhage with a FXa inhibitor last administered within 18 hours; for patients with an intracranial hemorrhage a Glasgow Coma Scale (GCS) score of greater than 5; and restricted prescribing privileges to critical care, emergency department, cardiology, and/or hematology attending physicians or their direct designee. The intent of the restriction criteria was to promote judicious prescribing due to concerns of adverse events, limited data availability, limited quantity on hand, and significant cost. The objective of this study was to evaluate adherence to institution restriction criteria and the clinical outcomes of treatment for patients for whom andexanet alfa is requested.

## METHODS

This was a retrospective cohort analysis of adult patients whom prescribers requested andexanet alfa for reversal of Xa inhibitor. This review was conducted at a single, 600-bed community teaching hospital from November 2018 to November 2019. The study design and methodology was approved by the Institutional Review Board.

Patients were included for analysis if a pharmacist received a request for the antidote within the predetermined time frame, regardless if approved or disapproved for administration. No patients were excluded from analysis.

Quality outcomes reviewed compliance to restriction criteria, anticoagulant agent for which reversal was requested, indication for reversal, and time to verification and administration. Clinical outcomes evaluated use of adjunctive blood products including factor product, ICU length of stay (LOS), hospital LOS, and hospital mortality. Safety outcomes evaluated incidence of thrombotic events.

Given the small number of patients expected in the overall analysis, descriptive statistics was used.

## RESULTS

During the first year on formulary, there were 16 requests for andexanet alfa, of which seven were denied. For the nine patients who received the medication, it was administered in the setting of an intracranial hemorrhage most frequently, 55% ( $n = 5$ ), followed by gastrointestinal hemorrhage 22% ( $n = 2$ ), and 22% ( $n = 2$ ) in the setting of an emergent surgical procedure (**Table 1**). Specific patient characteristics for andexanet alfa requests in the setting on intracranial hemorrhage are detailed in **Table 2**. The anticoagulant reversed by andexanet alfa was apixaban in 66% of cases and rivaroxaban in 34% of cases. Low-dose andexanet alfa was administered in 66.6% ( $n = 6$ ) of the patients. One patient, who's request for andexanet alfa was surgical reversal, received only the bolus dose of 400 mg in the operative setting according to anesthesia documentation. Average time from hospital presentation to reversal administration was  $241.8 \pm 199$  minutes. Timing of last direct oral anti-coagulant (DOAC) administration was unknown in a majority of patients (66.6%), and low-versus high-dose regimen of andexanet alfa was determined based largely on the DOAC agent and dose. The rate of mortality and thrombosis after andexanet alfa administration was 44.4% and 33.3%, respectively. Of the three patients who experienced a thrombotic event, the timing of thrombosis occurred at days 1, 3, and 9 post andexanet alfa administrations. Two thrombotic events were middle cerebral artery (MCA) infarcts, and one was left arterial appendage thrombosis.

Adherence to preapproved restriction criteria was 66.6% at our institution of the nine patients who

received the andexanet alfa. Of the three patients who did not meet the hospital criteria for andexanet alfa, two had baseline GCS scores of 3, but this restriction criteria was overruled by their provider. Both of these cases resulted in mortality. The other case was a patient with normotensive gastrointestinal bleed, who subsequently developed MCA ischemia post andexanet alfa administration, which also resulted in mortality. Surgical restriction criteria were ruled on a case-by-case scenario with the physician-in-charge and pharmacy management to deem appropriate for use. There were seven requests to pharmacists which were declined dispensing of andexanet alfa for lack of approved indication or adherence to restriction criteria. Of these, one patient experienced an in-hospital mortality due to succumbing to patients diagnosis, unrelated to bleeding complications. One thrombotic event occurred in the denial group, which involved an uncomplicated deep vein thrombosis of the lower extremity. Hospital restriction criteria followed the GCS exclusion criteria per the ANNEXA-2 trial. Additionally, hospital restriction criteria did not address the need for surgical reversal as the FDA approval for andexanet alfa did not address emergent surgery as an approved indication. Drug spending for andexanet alfa was approximately \$319,000, without respect of the new technology add on payment reimbursement capture. Drug spending avoided was \$203,280 due to implementation of restriction criteria.

## DISCUSSION

To our knowledge, this is the first single-center observation study of real-world patients who evaluated restriction criteria in combination with overall safety outcomes in patients with pharmacy requests for andexanet alfa reversal.

Given the extensive exclusion criteria in the ANEXXA-4 trial, development of criteria applicable for hospital use must attempt to develop guidance for generalizability for patients presenting as candidates for reversal. An important persisting question is the identification of patients most likely to benefit from reversal. Several other publications have reported real-world utilization data at single institutions. Two publications specifically evaluated real-world andexanet alfa use at their respective institutions and identified lower thrombosis risk than we identified in our evaluation and lower mortality rates (9, 10). Neither study detailed

institution-specific restriction criteria, and this may contribute to difference in patient outcomes based on those included for overall assessment. Giovino et al (10) had in-hospital mortality of 10.3%, and thrombotic event of 2.6%. Brown et al (9) has an in-hospital mortality of 24% and thrombotic event rate of 0% with no deaths attributed to thrombosis. The ANEXXA-4 trial excluded from the study who has planned procedure within 12 hours, leaving limited data to patients who may require reversal in the setting of emergent surgery and leaving institutions with the burden of optimizing administration in these cases. The use of andexanet for emergent surgical procedures should be approached with caution as the andexanet alfa trials identified rebound FXa levels following the end of infusion. The higher rate of mortality in our cohort may be attributed to partial adherence to restriction criteria, highlighting the need for stringent assessment of overall benefit in all patient scenarios. All patients in our subgroup who had andexanet alfa restriction criteria overruled experienced a hospital mortality, which speaks to the significance of developing a restriction criteria and finding best ways to minimize nonadherence. Because surgical patients were discussed in a case-by-case bases for risk benefit assessment with the lead attending and clinical pharmacy manager, these were not seen outside the restriction criteria. Our cohort had a higher rate of thrombosis, including thrombosis within 24 hours of administration resulting in mortality. In addition to serving as a modified human FXa decoy protein, andexanet alfa also binds to the endogenous tissue factor pathway. This is why thrombin levels are elevated for 22 hours after administration and explains the pro-coagulant effects observed in studies (6, 11). Our findings highlight that with the addition of andexanet alfa to formulary, a process for utilization not only minimizes unnecessary utilization of a medication that has a significant cost but also allows a risk benefit assessment to prevent adverse events. The multidisciplinary pharmacy and therapeutics committee worked to develop the restriction criteria at the institution. Restriction of andexanet alfa did not appear to negatively impact patients and showed the benefit of establishing a consensus based process.

Although our study offers a real-world retrospective comparison between patients treated and untreated with andexanet alfa, there are limitations to the analysis. It was a single center with small sample size. Those patients who were not treated with andexanet alfa were likely

experiencing less severe bleeding episodes or were less critically ill. A small number of patients in the andexanet alfa group received concomitant treatment with PCC, thus increasing the risk of thrombosis and mortality. This is a significant event to note for on-going healthcare prescriber education to prevent future patient safety events. No statistical analysis was planned or provided for these data as the two groups were very heterogeneous and small.

ANNEXA-4 was a multicenter, prospective, open-label, single-arm trial that evaluated patients with major bleeding, contributing to its approval by the FDA. Before approval of andexanet alfa, off-label treatment with 4-factor PCC (4F-PCC) was often used for the management of life-threatening hemorrhages associated with oral FXa inhibitors. New guidelines are now recommending the use of andexanet alfa as first-line therapy. Currently, only single-center retrospective reviews have compared differences of 4F-PCC or standard of care outcomes with andexanet alfa. A large, multicenter trial is needed to compare the benefits of andexanet alfa compared with standards of care.

## CONCLUSIONS

After 1 year of use at a community medical teaching institution, there was a higher rate of adverse events and mortality with the use of andexanet alfa than illustrated in clinical trials. This is potentially due to the use in a more severely ill population and lack of adherence to restriction criteria. This represents a single-center experience; thus, only minor subjective conclusions can be drawn until more clinical use data or a randomized controlled trial comparing with the previous standard of care, 4F-PCC, is available.

1 Department of Pharmacy, Saint Barnabas Medical Center, Livingston, NJ.

2 Ernest Mario School of Pharmacy-Rutgers University, Livingston, NJ.

This work was performed at Saint Barnabas Medical Center, RWJ-Barnabas Health System, 94 Old Short Hills Road, Livingston NJ 07039.

Drs. Sobolewski and Brophy were responsible for conception and design, analysis and interpretation, and drafting the article with final approval of submission. Drs. Choi and Opsha were responsible for conception and design, analysis and interpretation, and editing the article with final approval of submission.

The authors have disclosed that they do not have any potential conflicts of interest.



For information regarding this article, E-mail: Kristine.sobolewski@rwjbh.org

## REFERENCES

1. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883–891
2. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981–992
3. van Es N, Coppens M, Schulman S, et al: Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials. *Blood* 2014; 124:1968–1975
4. Santibanez M, Lesch CA, Lin L, et al: Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals. *J Crit Care* 2018; 48:183–190
5. Majeed A, Ågren A, Holmström M, et al: Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: A cohort study. *Blood* 2017; 130:1706–1712
6. ANDEXXA® (Coagulation Factor Xa (recombinant), Inactivated-Zhzo) [Package Insert]. South San Francisco, CA, Portola Pharmaceuticals, Inc. 2018
7. Connolly SJ, Crowther M, Eikelboom JW, et al; ANNEXA-4 Investigators: Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019; 380:1326–1335
8. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators: Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016; 375:1131–1141
9. Brown C, Scott, R, Sridharan M, et al: Real-world utilization of andexanet alfa. *Am J Emerg Med* 2020; 38:827
10. Giovino A, Shomo E, Busey KV, et al: An 18-month single-center observational study of real-world use of andexanet alfa in patients with factor Xa inhibitor associated intracranial hemorrhage. *Clin Neurol Neurosurg* 2020; 195: 106070
11. Tomaselli GF, Mahaffey KW, Cuker A, et al: 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017; 70:3042–3067